REMARKS

Claims 1-44 are pending. Solely in an effort to advance prosecution, claim 1 is amended to encompass potentially infringing subject matter. No new matter has been added. By the amendment, Applicants do not acquiesce to the propriety of any of the Examiner's rejections and do not disclaim any subject matter to which Applicants are entitled. *Cf. Warner Jenkinson Co. v. Hilton-Davis Chem. Co.*, 41 U.S.P.Q.2d 1865 (U.S. 1997). Further, Applicants reserve the right to file continuing applications to cover disclosed subject matter not encompassed by the currently pending claims.

Entry of the above amendment is believed to be proper under 37 C.F.R. § 1.116 because the amendment: (a) places the application in condition for allowance; (b) does not raise any new issues requiring further search and/or consideration; (c) does not present any additional claims without canceling a corresponding number of finally rejected claims; and/or (d) places the application in better form for appeal, should an appeal be necessary. Thus, entry is respectfully requested.

It is believed that each of the claims is now in condition for allowance. However, if anything further is required to place the claims in better condition for allowance, then the Examiner is invited to contact the undersigned representative at the telephone number listed below.

REJECTION UNDER 35 U.S.C. § 102

The Office Action maintains the rejection of claims 1, 2, 4, 6, 10, 20 to 24, 27 to 32 and 34 to 44 under 35 USC § 102(b) as allegedly anticipated by Schatz et al (U.S. Pat. No. 6,156,511). Applicants respectfully traverse this rejection.

Anticipation requires that ***all of the elements and limitations*** of a rejected claim are found within a single prior art reference. There must be no difference between the claimed invention and an applied reference's disclosure, as viewed by a person of ordinary skill in the field of the invention. *Scripps. Clinic & Research Foundation v. Genentech, Inc.*, 927 F.2d 1565, 1576 (Fed. Cir. 1991) (*citing Carella v, Starlight Archery and Pro Line Co.*, 804 F.2d 135, 138 (Fed, Cir. 1986); *RCA Corp, v. Applied Digital Data Systems, Inc.*, 730 F.2d 1440, 1444 (Fed. Cir. 1984)) (emphasis added).

Here, Applicants respectfully submit that there are significant differences between the claimed invention and Schatz that undermine the factual determination that Schatz describes the claimed invention within the meaning of 35 U.S.C. § 102. As further discussed below, Schatz does not disclose the features of non-covalent binding and *in vitro* expression of a plurality of DNA constructs, as presently claimed.

Specificity of binding. With respect to the claim language "capable of non-covalently binding directly or indirectly" in claim 1, the Office Action mistakenly suggested that in a situation where the peptide indirectly binds to the DNA target sequence, the peptide is not required to bind specifically to its target sequence. On the contrary, claim 1 part (b) explicitly requires that the expressed peptide is non-covalently linked to the DNA from which it was produced. As such, the binding of the peptide to the encoding DNA must therefore be specific in that the peptide must be non-covalently linked to a specific DNA molecule. Although indirect binding may encompass possible situations where, for example, the protein did not bind to the DNA itself but to an intermediate molecule bound to the DNA, the presence of such an intermediate molecule would not alter the specificity of the binding because the claims now require that the peptide is linked only to the DNA from which it was produced. In particular, amended claim 1 now refers to DNA encoding a peptide capable of non-covalently binding to the DNA target sequence and requires that the peptide is non-covalently linked to the DNA from which it was produced. As such, the recited encoded protein or peptide binds specifically to its encoding DNA molecule and not to any other DNA molecules in the mixture.

Cis-acting proteins. Schatz does not disclose or suggest the use of cis-acting DNA binding proteins. Although Schatz does disclose a large number of DNA binding proteins, these are not cis-acting DNA binding proteins. The Office Action asserts that Schatz "*clearly envisions a plurality of DNA vectors encoding proteins having cis-activity for a linker segment within the DNA vector from which it was encoded.*" On the contrary, the claimed invention requires that the DNA construct and its encoded protein are selected to have cis-activity. In other words, when the protein is expressed from the DNA construct, that protein molecule will bind only to the particular DNA molecule from

which it is has been expressed. Schatz does not disclose that the encoded protein is specifically targeted to the specific DNA molecule from which it has been expressed, or that the expressed protein will bind to the DNA molecule from which it was produced in preference to any other identical DNA molecules that are present, as required by the claims.

Applicants respectfully submit that a number of DNA constructs as defined in the claims may be expressed simultaneously in a single *in vitro* mixture. The expressed polypeptide molecules will each bind specifically to the particular DNA construct from which it is has been expressed. Thus, even though a number of DNA molecules and polypeptides are present in the same mixture, the polypeptides will be bound only to the DNA constructs from which they have been produced. By virtue of the features of the claimed invention, a plurality of different DNA constructs may be expressed simultaneously in a mixture *in vitro* without the risk of cross reactivity between different molecules. As discussed in the specification, a cis-acting system that utilizes the repA protein and the ori nucleotide sequence that is recognized by the repA protein in a cis-acting manner. This system can be utilized in accordance with the claimed method. For example, a plurality of different DNA sequences encoding different polypeptides of interest can be combined with the ori sequence and the sequence encoding the repA protein sequence. When such a plurality of DNA constructs are expressed together in a single mixture, even though each DNA molecule includes the same ori target sequence and each expressed polypeptide includes the same repA protein molecule, each repA molecule will be targeted to the ori target sequence in the specific DNA construct from which it has been expressed.

Further, if step (b) of the claimed method is carried out using any of the DNA binding proteins suggested by Schatz, there would be no way of targeting each expressed peptide to the specific DNA molecule from which it was produced. According to Schatz, any expressed polypeptide comprising a given DNA binding protein might bind to any DNA construct in the same mixture that comprises the relevant target sequence.

Schatz merely teaches that specificity of binding a polypeptide molecule to a particular type of DNA construct may be achieved by expressing each polypeptide within a cell. Within the confines of a cell, the expressed polypeptides may bind only to DNA target sequences that are present within the same cell. That is, if a single DNA construct is expressed in a cell, the expressed protein may bind only to that type of DNA construct because no other target sequences will be present. However, there is nothing in such a method that would target the expressed protein to only the specific DNA molecule from which it was expressed. Rather, any protein expressed within a cell may bind to any copy of the DNA target sequence within the same cell. At column 11, lines 27 to 35, Schatz states: "For best results with the present method, one should control the ratio of fusion proteins to vectors so that vectors are saturated with fusion proteins, without a vast excess of fusion protein. Too little fusion protein could result in vectors with free binding sites that might be filled by fusion protein from other cells in the population during cell lysis, thus breaking the connection between the genetic information and the peptide ligand". Thus, one of ordinary skill in art reading Schatz would realize that once the cells are lysed in order to obtain the construct-polypeptide fusions, any constructs that do not already have a polypeptide bound to them may then be bound by any other polypeptides that are present, such as polypeptides that are expressed in other cells from different constructs.

Indeed, one of ordinary skill in the art reading Schatz would realize that the disclosed method does not teach or suggest cis-activity, i.e. expressed peptides being only linked to the particular DNA molecules from which they were produced. If different DNA constructs are mixed together before expression in the Schatz method, any expressed polypeptide could bind to any DNA construct in the same mixture.

Moreover, Schatz merely teaches that the expression step is carried out in a cell to allow the polypeptide to bind to the DNA construct within that cell without the risk of cross-reactivity from other polypeptides, which include the same DNA binding protein. Only after this binding has been achieved are the cells lysed and the construct-polypeptide fusions harvested. Schatz, however, nowhere discloses the DNA constructs are or should be expressed *in vitro*, as required by the claimed invention. At

column 2, lines 41 to 45, Schatz clearly sets out the steps of transforming a host cell with the vector and culturing the host cell under conditions suitable for expression of the fusion protein. The subsequent paragraph goes on to explain that the cells are then lysed under conditions such that the fusion protein remains bound to the vector that encodes it. As such, this method must therefore be carried out in a cell and not *in vitro* as required by the present claims. Schatz relies on the use of the compartmentalized environment of a cell to achieve specific peptide-DNA binding. Schatz does not teach or suggest any way in which such specificity could be achieved without expression in cells. In particular, Schatz does not envisage using cis-activity in accordance with the present invention to ensure specificity of binding. See also claim 1 of Schatz et al patent, wherein step (c) specifies transforming host cells with the library of vectors to form transformed host cells. Those host cells are then cultured under conditions suitable for expression of the fusion proteins. Further step (d) of Schatz's method specifies that if the fusion protein comprises a potential DNA binding protein with affinity for a vector encoding the fusion protein, the fusion protein binds to the vector to form a complex. Again, Schatz nowhere discloses or suggests that the expressed protein only binds to the specific vector from which it was expressed. Rather, the expressed protein can bind to any vector in the same cell which includes the sequence to which the DNA binding protein will bind.

Further, Schatz merely teaches methods that rely on expression of DNA constructs within cells to separate different constructs from one another. Even if each different type of oligonucleotide construct is expressed in a different cell, the result will be that any fusion protein expressed in that cell may still bind to any vector in that cell that comprises the relevant DNA target sequence. In contrast, the claimed invention requires that the expressed protein molecule binds only to the specific DNA (e.g. vector) molecule that encoded it.

In short, Schatz is fatally mute as to at least the above-discussed claimed features or advantage realized therefrom. None of the DNA binding proteins disclosed in Schatz are cis-acting proteins, as required by the present invention. Applicants respectfully submit that the fundamental differences between the claimed invention and

Schatz are sufficient to undermine the purported factual determination of lack of novelty under 35 U.S.C. §102. *Kloster Speedsteel AB v. Crucible Inc.*, 793 F.2d 1565, 230 USPQ 81 (Fed. Cir. 1986). Based upon the foregoing, Applicants respectfully submit that the imposed rejection 35 U.S.C. §102(b) for lack of novelty over Schatz is not factually viable. Reconsideration and withdrawal of this rejection are respectfully requested.

REJECTION UNDER 35 U.S.C. § 103

The Office Action rejects claims 3, 5, 7, 8 and 9 under 35 U.S.C. § 103(a) as being unpatentable over the Schatz et al patent in view of Praszkier et al (1999). Applicants respectfully traverse this rejection.

As discussed in detail above, the claimed invention provides advantages that are neither suggested or envisaged by Schatz. The use of a cis-acting protein allows the method of the claimed invention to be carried out *in vitro*, without any need to express the DNA constructs within a cell. The claimed invention therefore provides a simplified method which can be used for expression in solution of a library of multiple different DNA molecules in such a way that the encoded peptides will be bound to the specific DNA molecules from which they have been expressed. This advantage could not be possible using the disclosed Schatz method because nothing in Schatz teaches or suggests that this advantage would be possible, let alone how it could be achieved.

"Before a conclusion of obviousness may be made based on a combination of references, there must have been a reason, suggestion, or motivation to lead an inventor to combine those references." *Pro-Mold and Tool Co. v. Great Lakes Plastics Inc.*, 75 F.3d 1568, 1573, 37 USPQ2d 1626, 1629 (Fed. Cir. 1996). "[E]vidence of a motivation to combine [references] need not be found in the prior art references themselves, but rather may be found in 'the knowledge of one of ordinary skill in the art or, in some cases, from the nature of the problem to be solved.'" *Dystar Textilfarben Gmbh v. C.H. Patrick Co.*, 464 F.3d 1356, 1366, 80 USPQ2d 1641, 1649 (Fed. Cir. 2006) (emphasis in original, quoting *In re Dembiczak*, 175 F.3d 994, 999, 50 USPQ2d

1614, 1617 (Fed. Cir. 1999)). However, "...rejections on obviousness grounds cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness." (*In re Kahn*, 441 E 3d 977, 988 (CA Fed. 2006). Applicants cannot overemphasize that the Office Action has not discharged the USPTO's initial burden of providing a basis upon which to predicate the legal conclusion that one having ordinary skill in the art would have considered the claimed invention obvious over the applied references.

Schatz does not teach or suggest the claimed method wherein the DNA construct and the encoded protein are have cis-activity. Schatz does not teach or suggest a method wherein a plurality of different DNA constructs are expressed together *in vitro* and each expressed peptide is non-covalently linked to the specific DNA molecule from which it was produced. It simply would not be possible to carry out such a method using the molecules or approach described by Schatz. Although Schatz discloses information regarding different types of DNA binding proteins that can be used in the methods described therein, there is no teaching, suggestion or motivation to replace the DNA binding proteins described therein with a cis-acting binding protein, as presently claimed. In view of the comprehensive Schatz disclosure, one of ordinary skill in the art would not have been motivated to substitute a different DNA binding protein that is neither mentioned nor suggested with the four corners of Schatz's disclosure.

Praszkier fails to remedy the deficiencies of Schatz. Praszkier merely teaches the so-called repA/ori system, but does not teach or suggest any particular practical or commercial use for such a system. One of ordinary skill in the art reading Schatz would have had no reason to consult Praszkier to try DNA binding proteins other than those described at column 7 of Schatz et al. Moreover, Praszkier does not teach or suggest that the repA/ori system could be modified to produce an *in vitro* peptide expression library, as presently claimed. Further, Praszkier nowhere suggests that the repA/ori system might be applicable to the type of methods described by Schatz et al. There simply is no teaching, suggestion or motivation in Praszkier to combine its teachings with Schatz, to obtain a method as currently claimed in which a DNA construct and

encoded protein are selected to have cis-activity and wherein a plurality of DNA constructs are expressed together *in vitro* in such a way that each expressed peptide is non-covalently linked to the specific DNA molecule from which it was produced.

The Office Action further rejects (a) dependent claim 33 under 35 U.S.C. § 103(a) as being unpatentable over the Schatz et al patent in view of Edwards and (b) dependent claim 25 under 35 U.S.C. § 103(a) as being unpatentable over the Schatz et al patent in view of Szostak and further in view of Mattheakis. For at least the reasons set forth above, Applicants respectfully traverse these rejections. In particular, claims 33 and 25 ultimately depend from claim 1 and merely recite more specific examples of the claimed method. Since the broader methods set out in the independent claims would not have been anticipated by or rendered obvious in view of Schatz, the more specific methods set out in dependent claims 33 and 25 are necessarily not anticipated nor rendered obvious over Schatz in view of any prior art reference, let alone in view of Edwards or in view of Szostak or further in view of Mattheakis, as applied in the Office Action.

"[One] cannot use hindsight reconstruction to pick and choose among isolated disclosures in the prior art to deprecate the claimed invention." *In re Fine*, 837 F.2d 1071, 1075 (Fed. Cir. 1988)). The inappropriateness of hindsight as a test of obviousness was, in point of fact discovered, and articulated lucidly, over three centuries ago, by Milton, who, in *Paradise Lost, Part IV*, L. 478-501, stated:

> *The invention all admired, and each how he*
> *To be the inventor missed; so easy it seemed,*
> *Once found, which yet unfound most would have thought,*
> *Impossible!*

The mere fact that the prior art may be modified in the manner suggested by the Office Action is not enough to have made the alleged modifications obvious unless the applied references suggested the desirability of the modification. *In re Fritch*, 23 U.S.P.Q.2d 1780, 1783-84 (Fed. Cir. 1992). The bottom line is that, for at least the above stated reasons, neither Schatz, Praszkier, Edwards, Szostak nor Mattheakis, taken singly or

improperly combined, disclose or suggest the features of the presently claimed invention. Applicants, therefore, respectfully submit that the imposed rejections under 35 U.S.C. §103 for obviousness is not factually or legally viable and, hence, hereby solicit reconsideration and withdrawal thereof.

CONCLUSION

If anything further could be done to place the above-captioned patent application in better condition for allowance (i.e., via Examiner's Amendment), then please contact the undersigned attorney at the telephone number listed below. Please grant any extension(s) of time deemed necessary for entry of this communication. The Commissioner is hereby authorized to charge any deficiency in the fee(s) filed, or asserted to be filed, or which should have been filed herewith (or with any paper filed hereafter) to Deposit Account No. **14-1140**. Please credit any overpayment of fees to such Deposit Account.

Respectfully submitted,

NIXON & VANDERHYE P.C.

Date: August 24, 2009

By: /Willem F. Gadiano/
Willem F. Gadiano
Reg. No. 37,136

901 North Glebe Road, 11th Floor
Arlington, VA 22203-1808
Telephone: (703) 816-4000
Facsimile: (703) 816-4100